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2. Journal of Immunotherapy, 1991 Aug, 10(4):267-277

3. International Journal of Cancer:
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8. Leukemia, 1996 Nov, 10(11):1765-1772

9. Experimental Hematology, Aug 1999, 27(8):1264-1270

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1491

Relationships Between Survival and Specific Host Defenses Assayed Ex Vivo Using a Curative Protocol of Adriamycin and Interleukin 2. R.L.X. Ho, P. Ujhazy, M.J. Ehrke and E. Mihich, Grace Cancer Drug Center, Roswell Park Memorial Institute, Buffalo, NY 14263.

Treatment with Adriamycin (ADM, 6 mg/kg, i.v., Days 1 and 8) plus interleukin 2 (IL2, 250U, i.p., bid, Days 9-40) increases the mean survival time of tumor (5 x 10^4 EL4 cells, i.p., Day 0) bearing C57BL/6 mice from 14 ± 2 days to > 60 days. This protocol was developed to exploit not only direct tumor cytotoxicity but also drug-induced immunomodulations identified in previous studies. In fact, the 60 day survivors can resist re-challenge by the same tumor indicating that a long-lasting immunity has been induced. Using this model of local administration of low dose IL2 in a chemoimmunotherapeutic protocol, the role of host antitumor defenses assayed ex vivo in relation to the in vivo measure of survival after inoculation of this weakly immunogenic tumor has been examined. Antitumor effector activities (natural killers, lymphokine activated killers with and without further in vitro stimulation by IL2, cytotoxic T lymphocytes, splenic macrophages, adherent and non-adherent peritoneal exudate cells) of mice treated in parallel with those in survival studies are measured at three time points during tumor progression. Data from these ex vivo assays show high correlation between elevated immune responses ex vivo and the treatment of the tumor bearing mice with ADM and/or IL2. These data are being analyzed to identify ex vivo assayable predictors of survival. Such predictors could be effectively used in monitoring therapeutic response and designing optimal protocols. (Supported in part by CA15142, CA24538, NCI USPHS and the gift of IL2 from DuPont.)

1492

The induction of lysis of renal cell carcinoma and other tumors by bispecific antibody reagents using natural killer (NK) cells TCRαβ and TCRγδ CTL as effector cells.

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We have characterized $TCR^-/CD3^-$ $TCR\alpha\beta^+/CD3^+$ and $TCR\gamma\delta^+/CD3^+$ CTL phenotypically and functionally. These populations are clearly distinct on the basis of their TCR gene rearrangements. This is also reflected by MHC-restricted regulatory and cytolytic functions. We have researched the regulation of lytic activity by the CD2,3,16 and framework TCRαβ and TCRγδ effector cell surface molecules. We have made use of bispecific antibody reagents recognizing activation sites on the effector cells on the one hand and (tumor) target associated antigens on the other. The results suggest that multi-chain activation processes are involved and that additional target cell "specific" structures play a role in interactions with retargeted cloned effector cells. The distinct effector cell types show differential activation states depending on the "CD" specificity of the bispecific reagents.

1493

Augmentation of antitumor effects of intraperitoneal (ip) interleukin-2 (IL-2) by monoclonal antibodies (MoAbs) and cyclophosphamide (CY). A.M.M. Eggermont[1] and P.H. Sugarbaker[2]. Depts. of Surgical Oncology, Rotterdam Cancer Institute[1], 3075 EA Rotterdam, the Netherlands; Winship Cancer Center[2], Emory University, Atlanta, GA 30322, USA.

The incubation of murine splenocytes in IL-2 gives rise to lymphokine activated killer (LAK) cells, which can lyse fresh tumor cells. Toxicity of IL-2 in vivo is high. Therefore ways to augment the antitumor effects of tolerable doses of IL-2 must be explored. We investigated the effects of MoAbs on LAK cytotoxicity in vitro and the use of CY in combination with IL-2 ± LAK in vivo in the treatment of established (day 3) ip tumor.

MoAbs : We have previously shown that in vivo induction of LAK by ip IL-2 is much higher in peritoneal exudate cells (PEC) than in splenocytes (SPL). Antibody dependent cellular cytotoxicity (ADCC) by in vivo generated LAK was investigated by administering C_3H mice ($H\text{-}2^k$) 2x100 KU IL-2/day ip, for 3 days. PEC and SPL were harvested and after adding anti-$H\text{-}2^b$ or anti-$H\text{-}2^d$ MoAbs their cytotoxicity was assessed in 4hr ^{51}Cr-release assays with tumor targets MCA-105 ($H\text{-}2^b$) and P815 ($H\text{-}2^d$). PEC-ADCC was ± 4 x higher than PEC-LAK lysis; SPL-ADCC and SPL-LAK were much lower.

Conclusion : MoAbs may be of particular interest for ip treatment regimens in combination with IL-2 ± LAK.

CY : We investigated the value of combining CY (50 mg/kg, day 3) with low dose IL-2 (2x10 KU/day, ip, day 3-7) ± LAK (10^8, ip, day 3) in the treatment of established ip tumor (MCA-105) in C57BL6 mice. In all experiments CY+IL-2+LAK therapy was superior to any single agent or other combination therapy, as assessed by ip tumor load on day 14. Also significant survival benefits were achieved (25% cures) after combination therapy. Conclusion : CY significantly augments antitumor effects of IL-2 and LAK in vivo.

1494

A comparison of the in vitro properties of expanded lymphocytes from tumor draining lymph nodes (DLN) tumor infiltrating lymphocytes (TIL) and autologous peripheral blood lymphocytes (PBL). Y. Skornick, S. Topalian, S.A. Rosenberg, Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

TIL have been used in immunotherapy trial and have shown encouraging therapeutic results in patients with Stage III melanoma. In vitro, many TIL populations derived from melanomas demonstrate lytic activity specific for the autologous tumor target, distinct from the non-specific activity of lymphokine activated killer cells (LAK). Regional or DLN are another source of lymphocytes which may be useful for immunotherapy. We have compared the in vitro properties of lymphocytes from DLN to autologous PBL and TIL grown from solid tumors from 10 patients; 2 melanomas, 4 breast carcinomas, 1 gastric cancer, 1 renal cancer 1 sarcoma and 1 lung carcinoma. PBL, TIL and DLN were grown in RPMI-10% human AB serum, 20% LAK cell culture supernatant, and 1000 u/cc rIL-2. Half of the cultures were restimulated with irradiated autologous tumor every 14 days (1:1 ratio). In all groups, tumor feeding enhanced proliferation. One melanoma TIL and DLN culture expanded for over 10 months. TIL and DLN proliferated longer and more rapidly than PBL. 8 of 10 early cultures of PBL, TIL and DLN contained greater or equal proportions of $Leu\text{-}2^+$ cells compared with $Leu\text{-}3^+$ cells. In long term cultures, an inversion of that ratio was seen. In short-term chromium release assays, specific lysis of autologous tumor was shown in tumor-fed TIL and DLN from 1 melanoma, 1 breast carcinoma and 1 lung carcinoma. Other cultures had non-specific lytic activity which usually correlated with $Leu\text{-}19^+$ positivity. Specific cytotoxicity against autologous tumor sometimes became apparent after prolonged culture and restimulation by autologous tumor. DLN have in vitro properties similar to TIL and may offer a useful immune reagent for cancer therapy.